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THE ACUTE KIDNEY OUTREACH TO PREVENT DETERIORATION AND DEATH – A LARGE PILOT STUDY FOR A CLUSTER RANDOMISED TRIAL.

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ABBREVIATIONS

CRRT Continuous Renal Replacement Therapy

ITU / ICU Intensive Therapy or Intensive Care unit

ABSTRACT

Background and objectives

The Acute Kidney Outreach to Reduce Deterioration and Death (AKORDD) trial was a large pilot study for a cluster randomised trial of AKI Outreach.

Design, Setting, Participants, and Measurements

An observational Control (Before) phase was conducted in two teaching hospitals (9 miles apart) and their respective catchment areas. In the Intervention (After) phase, a working hours AKI outreach service operated for the intervention hospital/area for 20 weeks, with the other site acting as a control. All AKI alerts in both hospital and community patients were screened for inclusion. Major exclusion criteria were patients who were end of life, or unlikely to benefit from Outreach, or lacking mental capacity, or already referred to the Renal team. The intervention arm included a model of escalation of renal care to AKI patients, depending on AKI stage. The 30-day primary outcome was a combination of death, or deterioration, as shown by any need for dialysis or progression in AKI stage. 1762 adult patients were recruited; 744 at the Intervention site during the After phase.

Results

A median of 3.0 non-medication recommendations and 0.5 medication related recommendations per patient were made by the Outreach team, a median of 15.7 hours after the AKI alert. Relatively low rates of the primary outcomes of death within 30 days (11-15%), or requirement for dialysis (0.4 – 3.7%) were seen across all four groups. In an exploratory analysis, at the Intervention hospital during the After phase there was an odds ratio for the combined primary outcome of 0.73 (95% CI 0.42, 1.26, $p = 0.26$).

Conclusions

An AKI outreach service can provide standardised specialist care to those with AKI across a healthcare economy. Trials assessing AKI outreach may benefit from focusing on those patients with "mid-range" prognosis, where nephrological intervention could have the most impact.

INTRODUCTION

Acute Kidney Injury (AKI) is known to occur in up to 20% of emergency admissions to hospital [1, 2] when the KDIGO or AKIN definitions are used.[3] Increasing AKI severity is closely associated with worsening mortality, length of stay and costs.[1, 4, 5] AKI has been recognised as leading to CKD and ESRD, with the risk rising with increasing severity of AKI.[6, 7]

Care of patients who develop AKI has long been recognised as being suboptimal,[8] a finding present even in recent literature.[9, 10] A seminal National inquiry into AKI care in the UK showed significant flaws in AKI care, and suggested that 14% of all cases AKI were avoidable, with 31% of post admission AKI being avoidable.[9] This led to the introduction of a National alert system for AKI in England and Wales.[11]

There is observational data suggesting that delayed referral and nephrology consultation is associated with poorer outcomes in critical care[12-14] and in general hospital admissions.[15] The medical emergency team (or critical care outreach) was developed to detect and treat deterioration in hospitalised patients at an earlier stage, based on vital signs monitoring.[16] However, in spite of the potential benefits, a major trial of a rapid response system failed to show improved outcomes.[17]

With the advent of sophisticated laboratory information systems and more frequent creatinine testing it has been possible to develop alerts that warn clinicians of the development of possible AKI.[18-21] However, the implementation of a “standalone” alert system for AKI did not improve outcomes.[22] We hypothesised that “Outreach”, combining the use of alerts together with early Nephrology consultation, could improve outcomes in AKI. We[23] and others[24] have tested the concept in small scale. We present the results of the AKORDD trial, a large pilot study of AKI Outreach.

METHODS

Study design and participants

The trial protocol has been published.[25] In brief, we ran a study of a complex multifactorial intervention,[26] as a pilot for a cluster randomised trial. Using a Before and After study design with concurrent controls[27], we piloted the Outreach service to AKI patients. Intervention and control patient recruitment was based on defined geographical (postcode) areas. The 2011 UK census gave the usual resident population in the intervention and control areas as 306,309 and 364,234, respectively. The study was approved by the National Research Ethics Service (Reference: 14/EM/0184), and registered at ClinicalTrials.gov (NCT02398682). It was funded by the Research for Patient Benefit programme of the UK National Institute for Healthcare Research (PB-PG-1111-26038). The study was focused on providing AKI Outreach to clinicians. We wrote to all enrolled patients giving them an “opportunity to dissent,” or “opt out” of the study.

Patients with an electronic AKI alert[11, 28] were screened, and inclusion and exclusion criteria were applied (figure 1, see [25]). The inclusion criteria were: an adult (≥ 18 years) patient with an Alert (stages 1 to 3), due to AKI detected from a serum creatinine from Heartlands or Good Hope Hospitals, or their associated postcodes for community patients. Major exclusion criteria included these: deceased at the time of Outreach team intervention; already referred to Nephrology or accepted for dialysis by the Renal Unit; the terminal phase of malignancy or end stage major organ disease; and lacking mental capacity.[25] Recurrent AKI was not part of the analysis, and patients could not be enrolled in more than one phase.

The trial had two phases and four groups (two during each phase, supplementary figure 1). During the 2-month Before phase in April to May 2015, patients in the two groups (Heartlands and area, and Good Hope and area) were observed for trial outcomes, without any intervention, thus defining outcome with good standard care.

During the 5-month 'After' phase in June to November 2015 the intervention was delivered to the intervention group (Heartlands and area) only, and patients treated at Good Hope hospital and area continued to receive standard care. At Heartlands the intervention was provided for AKI patients in secondary and primary care, described elsewhere.[25] In brief, there was a stage based approach to AKI outreach[25], using a working-hours team consisting of a Renal Fellow, a Critical Care outreach nurse with AKI experience, and a Consultant Nephrologist. For patients in primary care the call went to their General Practitioner.. We assessed "Fidelity" (adherence to recommendations[27]), as part of a review of paper records for our health economic sub-study.

Outcomes

Primary outcomes

The purpose of this study was to determine likely outcome rates in and assess the feasibility of a full cluster randomised study[25]. The primary outcome was a composite of:

- A. All-cause death within 30 days;
- B. Any need for dialysis (intermittent haemodialysis or continuous renal replacement therapy) within 30 days;
- C. Progression of AKI stage after enrolment, and without dialysis within 30 days after the alert (stage progression is stage 1 deteriorating to 2 or 3; stage 2 deteriorating to stage 3).

Secondary outcomes

These events as given in the discharge letter:

- 1. Cause of AKI: new glomerulonephritis or new urinary obstruction diagnosis.
- 2. Complication of AKI not requiring dialysis: new pulmonary oedema, uraemia ≥ 30 mmol/L or hyperkalaemia (≥ 6.0 mmol/L).

Sample size

The sample size was calculated with the intent of estimating uncertainty of outcomes, to inform the design of the future cluster trial. Our previous work suggested that the combined outcome would be seen in about 40% of patients having an alert. With a sample size of >1000 (intervention group—Heartlands and area, after phase), a 95% CI of width 6% (37% to 43%) can be calculated. A sample size of 370 (control group—Good Hope and area, after phase) will allow us to produce a 95% CI of width 10% (35% to 45%). To limit multiple significance testing in a pilot study, this was not done for outcomes other than those specified above.

Statistical analysis

Analyses were used to describe the characteristics of participants in each location and phase of the study, with appropriate summary measures reported. The primary outcome was estimated for each study site and phase of the study and 95% confidence intervals for these estimates were provided also. Descriptive statistics were also provided for secondary outcomes by group and phase of the study. Exploratory analyses were undertaken, using a logistic regression model (with the primary composite outcome and components of this used in separate models) to obtain adjusted estimates of differences between study areas and phases (an interaction term was used to estimate the effect of the intervention in the active phase).

RESULTS

Recruitment

The trial recruitment is shown in two Consort diagrams (Figure 1). Recruitment was based on geographical area, and considerable numbers of community patients were excluded simply because they were out of area for either hospital. The results of 1762 eligible patients are presented here. Our health economic study has been published.[29]

Baseline characteristics

Most (82.1%) enrolled patients were in hospital at the time of enrolment, 17.6% in a community location (including outpatients), and 0.3% in another or unspecified location. Participants for all four groups in the study were typical of the spectrum of the AKI patients. However, the control hospital serves a more affluent but ageing population, in a less ethnically diverse area of Northeast Birmingham. The intervention hospital is in a poorer area of East Birmingham with a somewhat younger, more ethnically diverse population. Those in the control hospital were older, with a higher proportion of women and patients of European origin (see Table 1). All groups had a similar spread of AKI stages and non-renal, non-malignant comorbidities.

Dynamic patient flows in entire cohort

At enrolment, current patient residence was: living in own home 1630 (92%); in sheltered home 58 (3.3%), in residential home 26 (1.5%), and in Nursing home, or other facility (e.g. Prison or Mental Health) 48 (2.7%). At the time of the Alert 1445 (82.0%) were on a hospital ward (including the emergency department), but altogether 1540 (87.4%) were admitted within 14 days of the alert. Of the 1540 admitted patients, 195 (12.7%) died in hospital. Of the 1345 patients discharged alive, 92 (6.8%) were discharged to a higher level of care than they required at admission, 2 (0.1%) were discharged to a lower level of care, and the remainder showed no change in care at discharge, based on residence alone. The median (IQR) length of stay from enrolment to discharge (which was not total length of stay) was 6.5 (2.5 – 13.7) days. Two-hundred-and-thirty (14.9%) of the 1540 admitted patients were enrolled on the day of discharge or after discharge, showing the rapid

movement of patients out of the hospital system. 59 of the 744 (7.9%) in the intervention phase at the intervention hospital were enrolled on the day of discharge or after discharge.

Causes and course of acute kidney injury

The four groups showed a similar range of causes of AKI, notably for the top trio of hypovolaemia, sepsis and drug toxicity (table 2). Only the intervention hospital has inpatient urology care, and it had a higher proportion of patients with obstructive or post-renal causes for AKI, likely for that reason.

Interventions in the After phase at the Intervention Hospital (table 3)

326 of 744 (43.8%) patients had their laboratory AKI alert issued in working hours, when the team was available, whereas 56.2% of alerts were issued out of hours. The interventions were delivered at a median of 15.7 hours (interquartile range 3.9 to 37.2) after the time of the AKI alert. In the active intervention phase at the Intervention Hospital, a median of 3 (interquartile range 2-3) interventions were recommended per patient. These were a range of recommended interventions across best practice nephrological care for the patients. Recommendations to record weights appeared under-utilised, compared to urine output monitoring. Amongst medication changes, 551 of 830 (63%) stoppages of drugs had been made by the primary clinical team due to AKI. 329 (37%) further changes were recommended by Outreach team (0.5 per patient), mainly “Stop” recommendations.

Primary and secondary outcomes

Relatively low rates of the primary outcomes of death within 30 days (11-15%), or requirement for any renal replacement therapy (RRT, 0 – 3.1%) were seen across all four groups (table 4). AKI stage progression occurred at a rate of 4-8%. The challenges of timely intervention were shown by the finding that overall 4% of all enrolled patients had stage progression before enrolment, and 7% had progression after enrolment. Similarly, 5 patients required CRRT in ITU/ICU before enrolment, and overall 30 patients required RRT after enrolment. The combined primary outcome of death, dialysis or stage deterioration showed no difference between groups, with rates of 16-19%.

In an exploratory analysis, after Multivariate adjustment to outcomes amongst the four groups, adjusting for age, sex, ethnicity, location of residence, hospital ward location, and total non-Renal non-malignant comorbidities, the interaction of the Intervention hospital during the After phase showed a lower odds ratio for the combined primary outcome, OR 0.73 (95% CI 0.42, 1.26, $p = 0.26$). Low rates of secondary outcomes, based on discharge diagnoses, were seen (new glomerulonephritis, urinary tract obstruction, pulmonary oedema, hyperkalaemia (≥ 6.0 mmol/L) or uraemia, table 4).

Fidelity

A non-random sample of twenty patients was separately consented for this sub-study at the Intervention hospital in the After phase. For these patients a median of four (interquartile range 2 – 5) recommendations (non-drug and drug) were made, for which an extensive paper notes review showed that 64 of 78 (82%) were adhered to. Failure to carry out urine dipstick testing accounted for 5 of 14 (36%) recommendations that were not implemented.

Stage 3 patients in the Intervention phase

Our protocol called for stage-based care, as recommended by KDIGO. For patients with a stage 3 alert in the Intervention Hospital during the Intervention phase, this included a ward visit by a Nephrologist, and a clinic visit to a Nephrologist after discharge for survivors. Overall there were 107 patients who reached stage 3: 66 with a stage 3 alert at enrolment; 38 who later had a stage 3 alert after enrolment; 2 who were stage 3 only by virtue of needing RRT, and 1 who became stage 3 after the intervention phase had ended. Including consults by Nephrology colleagues, we carried out a ward visit on 85 of the 104 patients (82%) who had a stage 3 alert during the study.

28 of the entire group of 107 (26%) died during their hospital stay; 5 were discharged with end of life care. So regarding clinic visits for the 104 with a stage 3 alert during the study (figure S3), 33 had died or were end of life; 44 were seen by the AKORDD team; 14 were seen by Nephrology or a specialist directly managing the cause of AKI; 5 did not attend their appointment; and we were unable to contact/agree an appointment for 8 patients. Including appointments by Nephrology or other relevant specialists, appointments were achieved in 58 of 71 survivors (82%).

DISCUSSION

Referral of patients with AKI is a complex process, typically relying on the hospital or primary care team to refer to their local nephrology service. The AKORDD study was a large pilot for a Cluster randomised study, aiming to provide Outreach to the primary clinical teams managing eligible patients with AKI, either in primary or in secondary care. Our study was 4 × [23] to 10 × [24] the size of previous studies, and the first with concurrent controls. Using an “opt out” form of consent, patients were chiefly excluded for predictable reasons: they had already been seen or referred to Nephrology; early death of very sick patients before the intervention could be delivered, or patients lacking capacity (including those with advanced dementia) to understand the opt out consent. With large numbers of patients anticipated and recruited across a large geographical area, the intervention was chiefly delivered by phone to a member of the clinical team responsible for continuing care of the patient, in addition stage 3 AKI patients were visited by a Nephrologist. There have not been any trials of Nephrology follow-up for stage 3 survivors, but rather observational studies suggesting benefit,[30] and ours is the first study to systematically attempt this. Amongst the interventions advised, many were relatively simple interventions for the care of the AKI patient, consistent with the known limitations of acute care for AKI patients[8] and previous experience.[23, 24] The interventions were largely delivered in a timely fashion, at a median of about 16 hours after the Alert, comparable to 13[24] - 14[23] hours in previous much smaller studies. The patients were predominantly elderly and multimorbid, requiring a wide range of different interventions. A moderate number of interventions were advised, and interventions need to be further developed to address common comorbidities co-existing with AKI, condition by condition. It is known in stroke care that the delivery of a higher number of interventions is associated with better outcomes.[31] We also carried out qualitative work which highlighted the widely disparate assistance desired by the targeted primary teams, ranging from critical care through to primary care (not shown). Stage based care for AKI across a health economy is challenging, with frequent patient movement between the community and hospital care or vice versa, and with the frail elderly survivors of AKI. Ward and clinic visits were a logistical challenge, particularly for those patients who had a Stage 3 alert at any time after enrolment (figure S3). We

achieved, with Nephrology colleagues, ward visits to 82% of stage 3 patients during the intervention phase. Outpatient follow-up of sick survivors was also challenging (albeit successful), even with the use of a virtual clinic and telephone discussions with patients. We achieved, together with Nephrology and other relevant specialist colleagues, clinic follow-up of 82% of survivors.

The outcomes of death or need for dialysis showed a lower than expected frequency, possibly partly due to the exclusion of some of the sickest patients (above). The usage of dialysis was low, consistent with the 3 to 4% usage seen in our studies in 2008[19] and 2009,[23] although higher than the 1% incidence in one other study, carried out in the US in 2008-9.[24]

Strengths and limitations

Our study has several strengths. The setup of the Outreach team was realistic, given the large numbers of patients and working hours nature of the team. Providing a dedicated, seven day a week team, separate from the Nephrology team, including out-of-hours, was not feasible. Nevertheless, the Outreach provided dealt with a group of patients very similar to those seen by consulting Nephrologists, albeit on a much larger scale. This was the first large scale study to use Outreach across a well-defined healthcare economy, including both primary and secondary care. This required the introduction of AKI alerts[28] in both of these sectors in the NHS locally. The linking of an AKI alert trigger to outreach response has demonstrated that specialist nephrology recommendations can be conveyed to a wide range of healthcare staff managing AKI, in a timely and effective way. The stage-based approach with more intensive intervention for stages 2 and 3 and the AKI follow up clinic were very largely successful.

The limitations of the trial were mainly inherent in the design of the pragmatic study. Stage 1 AKI patients had a “one-time” outreach intervention, necessitated by their very considerable numbers. However, stages 2 and 3, including those with stage progression, did receive more intensive intervention[25]. Within the control group it was not feasible to measure time to Nephrology referral to a number of Nephrologists, working outside the trial. We did not determine possible recommendations for control patients during the trial, as the call needed to determine these would have been an intervention. As a pilot study it lacked randomised clusters, so the patients in the control and intervention area were subtly different. A disadvantage of the pragmatic nature of the

intervention, with a modest team working “in hours”, is that the intervention was inevitably sometimes delivered after the AKI was recovering or resolved. In conclusion, we found that AKI outreach can be delivered to large numbers of patients across a healthcare economy or area, in a reasonably timely fashion using a working hours team.

Trial evidence to support a clear set of single interventions that can be usefully combined to improve AKI outcomes is lacking. A large prospective National audit of stage 3 acute kidney injury in England in 2012 looked at care processes associated on multivariate analysis with outcome.[32] It found that dipstick urinalysis, medication review, discussion with a nephrologist and acceptance for transfer to a renal unit were associated with higher survival, but not early review by a senior doctor, acceptance for transfer to critical care or requirement for renal replacement therapy. Our trial focused on delivery of the care processes known to be associated with improved outcome.

Our trial was not powered to show a difference in outcome rates, highlighting the larger number of clusters and patients needed to demonstrate whether Outreach can affect outcomes. Such a cluster randomised trial might include a six or seven-day service, to reduce the time to intervention further and mitigate at least some of the “weekend effect,”[33] although the exact nature of this effect remains unclear.[34] Future studies could concentrate on mid-range to higher risk patients, for example those that are stage 2 or 3 AKI.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to disclose. The results in this paper have not been published previously in whole or part, except in abstract format.

CONTRIBUTIONS OF THE AUTHORS

MET, GDP and AS designed the study; MET, TA, RMT and JB ran the study; MET, TA and AS analysed the study; all authors contributed to the manuscript.

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TABLES AND FIGURES LIST

- Table 1. Baseline characteristics of the four trial groups.
- Table 2. Causes and course of acute kidney injury.
- Table 3. Drug and non-drug interventions.
- Table 4. Primary and secondary outcome rates.
- Figure 1. Consort diagrams for the Before and After phases.

TABLE 1: BASELINE CHARACTERISTICS OF THE FOUR GROUPS IN THE AKORDD STUDY.

1 Kruskal Wallis test; 2 Chi square test; 3 Independent home living or sheltered accommodation or equivalent 4 Including Emergency department; 5 Non-malignant, non-renal comorbidities

GROUP	CONTROL HOSPITAL: 'BEFORE' PHASE	INTERVENTION HOSPITAL: 'BEFORE' PHASE	CONTROL HOSPITAL: 'AFTER' PHASE	INTERVENTION HOSPITAL: 'AFTER' PHASE	<i>p</i>
	N=239	N=382	N=397	N=744	
Age (years); mean (SD)	72.7 (16.4)	69.4 (17.9)	72.6 (15.3)	69.4 (16.6)	0.002 ¹
Sex (male); n (%)	108 (45)	218 (57)	182 (46)	435 (58)	<0.001 ²
Ethnicity (European); n (%)	226 (95)	271 (71)	361 (91)	578 (78)	<0.001 ²
Residence (at home ³); n(%)	222 (93)	368 (96)	384 (97)	717 (96)	0.27 ²
Hospital ward location ⁴ ; n (%)	192 (80)	306 (80)	291 (73)	657 (88)	<0.001 ²
Non-malignant comorbidities ⁵ ; mean (SD)	1.24 (1.09)	1.20 (1.10)	1.08 (1.07)	1.24 (1.13)	0.13 ¹
AKI stage 1; n (%)	179 (75)	275 (72)	290 (73)	553 (74)	0.85 ²
AKI stage 2; n (%)	33 (14)	63 (16)	68 (17)	125 (17)	
AKI stage 3; n(%)	27 (11)	44 (12)	39 (10)	66 (9)	

TABLE 2: CAUSES AND COURSE OF ACUTE KIDNEY INJURY IN THE FOUR GROUPS IN THE AKORDD STUDY.

GROUP	CONTROL HOSPITAL: BEFORE STUDY n = 239	INTERVENTION HOSPITAL: BEFORE STUDY n = 382	CONTROL HOSPITAL: AFTER STUDY n = 397	INTERVENTION HOSPITAL: AFTER STUDY n = 744
Major causes of AKI¹				
Hypovolaemia	137 (57.3)	235 (61.5)	248 (62.5)	471 (63.3)
Sepsis	81 (33.9)	123 (32.2)	145 (36.5)	283 (38.0)
Drug toxicity	114 (47.7)	179 (46.9)	218 (54.9)	386 (51.9)
Post renal	18 (7.5)	45 (11.8)	23 (5.8)	83 (11.2)
Surgical	20 (8.4)	45 (11.8)	38 (9.6)	84 (11.3)
Creatinine (Cr) $\mu\text{mol/L}$				
Baseline Cr	95 (44) [239]	102 (74) [382]	93 (47) [397]	92 (37) [744]
Alert Cr	194 (197) [239]	190 (126) [382]	177 (107) [397]	174 (102) [744]
Peak Cr	209 (203) [239]	217 (160) [382]	192 (122) [397]	194 (121) [744]
30-day Cr ²	109 (71) [205]	118 (88) [338]	120 (77) [337]	108 (59) [654]
90-day Cr ²	105 (54) [184]	118 (109) [313]	113 (72) [307]	102 (46) [616]
182-day Cr ²	106 (60) [172]	118 (105) [291]	113 (85) [292]	102 (46) [566]
365-day Cr ²	107 (62) [161]	122 (125) [253]	120 (105) [270]	105 (49) [524]
CKD EPI eGFR mL/min/1.73m²				
Baseline eGFR	67 (24) [239]	71 (28) [382]	70 (26) [397]	73 (26) [744]
Alert eGFR	35 (17) [239]	37 (19) [382]	36 (18) [397]	39 (19) [744]
Nadir eGFR	32 (17) [239]	34 (21) [382]	34 (18) [397]	36 (19) [744]
30-day eGFR ²	62 (26) [205]	64 (30) [338]	58 (27) [337]	65 (28) [654]
90-day eGFR ²	63 (26) [184]	66 (29) [313]	60 (26) [307]	67 (26) [616]
182-day eGFR ²	63 (26) [172]	67 (30) [291]	62 (26) [292]	68 (26) [566]
365-day eGFR ²	63 (26) [161]	67 (30) [253]	62 (27) [270]	66 (27) [524]

All major contributory factors were listed for each patient. Patients may have more than one cause of AKI, as determined from discussion with primary team and the electronic patient record. Figures are number (percentage) of patients or mean (SD) [number of survivors].

1 Determined by Outreach team after discussion with primary team. 2 Last observation carried forward.

TABLE 3: INTERVENTIONS IN THE ACTIVE PHASE AT THE INTERVENTION SITE.

INTERVENTION	INTERVENTION HOSPITAL: AFTER STUDY n = 744
Bedside monitoring, oxygen and fluids	
Urinalysis	609
Formal urine output monitoring	104
Standing heart rate and BP	29
Daily weights	8
High flow oxygen	2
Start or increase intravenous fluids	156
Start or increase oral fluids	72
Decrease or stop intravenous fluids	7
Other fluid recommendation	23
Drug recommendations	
Stop	329*
Start or restart	24
Avoid planned drug (e.g. contrast)	15
Previously stopped by primary team	551
Pathology tests	
Repeat Urea, creatinine, electrolytes or advice about frequency of testing	684
Venous bicarbonate	36
Venous lactate	19
Arterial blood gases	2
Full blood count	5
Clotting	2
Blood cultures	3
Urine microscopy and culture	16
Imaging	
Avoid contrast (if being considered)	17
Urinary tract ultrasound	18
Other imaging recommendation	8
Patient pathway	
Urgent Renal outpatient appointment	12
Admit to hospital	4
Senior medical review	12
Transfer to Renal Inpatient care	6
Refer to Critical Care for transfer	1
Allied Health Professional referral and discharge	
Nutrition review – refer to dietician	26
Physiotherapy	7
Discharge planning	1

There were a median (IQR) of 3.0 (2.0 – 3.0) non-drug recommendations per patient in the Intervention group. * “Stop” recommendations: Renin-angiotensin system agent 115 (35%), diuretic 59 (18%), other antihypertensives 50 (15%), non-steroidal anti-inflammatory agent 48 (15%), all other stop recommendations 57 (17%).

TABLE 4: PRIMARY AND SECONDARY OUTCOMES. ¹Chi square test; ² Fisher's exact test (two sided); *One sided 95% CI

	'BEFORE' PHASE		'AFTER' PHASE		
	CONTROL	INTERVENTION	CONTROL	INTERVENTION	p
Primary outcomes	n = 239	n = 382	n = 397	n = 744	
30-day mortality n/N	34/239	44/382	60/397	90/744	
% (95% CI)	14.2 (10.1, 19.3)	11.5 (8.5, 15.2)	15.1 (11.7, 19.0)	12.1 (9.8, 14.7)	0.37 ¹
Stage progression	10/239	31/382 (8.1)	23/397	64/744	
% (95% CI)	4.2 (2.0, 7.6)	8.1 (5.6, 11.3)	5.8 (3.7, 8.6)	8.6 (6.7, 10.9)	0.071 ¹
Any RRT (CRRT or HD)	0/239	12/382	5/397	13/744	
% (95% CI)	0.0 (0.0, 1.5)*	3.2 (1.6, 5.4)	1.3 (0.4, 2.9)	0.4 (0.9, 0.3)	0.07 ¹
Combined primary outcome	39/239	72/382	73/397	141/744	
% (95% CI)	16.3 (11.9, 21.6)	18.8 (15.0, 23.1)	18.4 (14.7, 22.6)	19.0 (16.2, 22.0)	0.83 ¹
Secondary outcomes					
New glomerulonephritis diagnosis	1/239	7/382	7/397	12/744	
% (95% CI)	0.4 (0.0, 2.3)	1.8 (0.7, 3.7)	1.8 (0.7, 3.6)	1.6 (0.8, 2.8)	0.55 ²
New Urinary tract obstruction diagnosis	9/239	28/382	3/397	19/744	
% (95% CI)	3.8 (1.7, 7.0)	7.3 (4.9, 10.4)	0.8 (0.2, 2.2)	2.6 (1.5, 4.0)	0.01 ²
New Pulmonary oedema complication	9/239 (3.8)	24/382 (6.3)	1/397 (0.3)	14/744 (1.9)	
% (95% CI)	3.8 (1.7, 7.0)	6.3 (4.1, 9.2)	0.3 (0.0, 1.4)	1.9 (1.0, 3.1)	0.03 ²
New hyperkalaemia (≥ 6.0 mmol/L)	0/239	16/382 (4.2)	8/397 (2.0)	4/744 (0.5)	
% (95% CI)	0.0 (0.0, 1.5)*	4.2 (2.4, 6.7)	2.0 (0.8, 3.9)	0.5 (0.1, 1.4)	0.55 ²
New Uraemia	3/239 (1.3)	19/382 (5.0)	0/397	9/744 (1.2)	
% (95% CI)	1.3 (0.3, 3.6)	5.0 (3.0, 7.7)	0.0 (0.0, 0.9)*	1.2 (0.6, 2.2)	<0.001 ²

Figure 1. Consort diagrams for the Before and After phases.

(see separate file)

SUPPLEMENTAL MATERIAL

FIGURE S1: Trial Design – reproduced with permission.

FIGURE S2. Stage 3 AKI patients during intervention phase at intervention hospital.

